Management of chronic pancreatitis

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Cite this as: *BMJ* 2024;384:e070920
http://dx.doi.org/10.1136/bmj-2023-070920

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ABSTRACT

Chronic pancreatitis results from repeated episodes of pancreatic inflammation and associated fibrosis leading to the loss of functional exocrine and endocrine pancreatic function. The disease is manifested by abdominal pain, deterioration in quality of life, food maldigestion and malabsorption, diabetes, and an increased risk for pancreatic adenocarcinoma. This review summarizes the latest evidence on the diagnosis and management of chronic pancreatitis and its manifestations. In particular, this review discusses advances in understanding of the role of genetic disorders in the mechanisms of the disease and surgical options for patients refractory to medical therapy. Furthermore, clinical trials are under way to develop medical therapeutics.

Introduction

Chronic pancreatitis is a "suffering" disorder owing to pain and related reduction in multiple quality of life measures resulting from a fibroinflammatory response to injury in the exocrine pancreas. In addition to pain, chronic pancreatitis can lead to exocrine and endocrine failure (that is, exocrine pancreatic insufficiency and diabetes) and an increased risk for pancreatic cancer. No cure for chronic pancreatitis exists, but understanding of the mechanisms of the disorder is increasing and significant progress in management has been made. The objective of this review is to summarize the latest information on chronic pancreatitis and provide suggestions for further research to improve the management for patients with this disease.

Sources and selection criteria

We searched PubMed from 1980 to April 2022 for systematic reviews, meta-analyses, randomized controlled trials (RCTs), and international guidelines in the English language, using the search term "chronic pancreatitis". This found 23 457 articles and 285 clinical trials. We expanded the search to include observational studies on the topics of severity, management and treatment, interventional techniques, and complications of chronic pancreatitis. We excluded case reports and case series with fewer than 25 patients. We prioritized studies by design in the order noted above, national guidelines, and high quality studies with large patient numbers. In addition, we reference published guidelines and consensus statement for chronic pancreatitis.

Epidemiology

The prevalence of chronic pancreatitis is about 50 per 100 000 people.[1] This information comes mostly from survey and health system database studies in the United States,[1-5] Japan,[6] China,[7 8] India,[7 9] and Europe.[10 11] Usually, chronic pancreatitis develops from recurrent episodes of non-gallstone acute pancreatitis. Variations in prevalence occur between regions and are based on differences in the causes of acute pancreatitis. That is, populations with high rates of gallstone acute pancreatitis compared with non-gallstone acute pancreatitis have a lower prevalence of chronic pancreatitis, whereas populations with a high rate of non-gallstone acute pancreatitis (that is, due to alcohol misuse) have a higher prevalence of chronic pancreatitis. Other factors that contribute to variation in prevalence estimates across populations include differences in approaches to establish the diagnosis and study methods used for reporting.

Natural history

The original descriptions of the pathologic sequence of chronic pancreatitis come from the historical case series of 29 patients published in 1946.[12] The authors proposed that episodes of repeated acute pancreatitis can lead to chronic pancreatitis on the basis of their histological findings in patients. This progression of findings of acute inflammatory necrosis to fibrosis with calcification is referred to as the necrosis-fibrosis theory. Further details about this progression have been recorded with case series, histological analyses, consensus reports, and a subsequent mechanism based model.[13-17] These mechanisms are described in this review. In clinical practice, tissue is rarely available because of risks associated with biopsy, so the definitive diagnosis of chronic pancreatitis relies on advanced imaging or advanced endoscopic techniques identifying ductal abnormalities, parenchymal fibrosis, calcifications, and other findings such as ductal stones or pseudocysts.[1 18 19] However, in clinical practice, the term acute-on-chronic pancreatitis is often used to describe recurrent relapses of pancreatitis symptoms consistent with the necrosis-fibrosis theory. Recently, a consensus definition from a group of international

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pancreatitis experts described acute-on-chronic pancreatitis with worsening of the inflammatory process associated with chronic pancreatitis, resulting in a deterioration of the patient's clinical condition and increased pancreatic pain.[20]

Because these diagnostic entities are not widely available, especially in poorly resourced countries, the exact prevalence of chronic pancreatitis is unknown. That is, determination of the true prevalence of chronic pancreatitis requires the complex assessment that is necessary to establish the diagnosis. Consequently, most series reporting the prevalence of chronic pancreatitis do so from the perspective of hospital admissions and varying levels of expertise in establishing the diagnosis, so an underestimate of the true disease prevalence in the entire population is likely.[21]

One frequently cited population based study from the Mayo clinic examined 106 cases of chronic pancreatitis between 1977 and 2006.[4] Half of the cases were caused by alcohol and 58% were in men, with the age and sex adjusted incidence rate being 2.9 cases/100 000 person years between 1977 and 1986. The incidence increased to 4.4/100 000 between 1997 and 2006. These data are somewhat old, and the increasing prevalence noted more than a decade and a half ago suggests that the current prevalence of chronic pancreatitis is higher than previously thought.

Chronic pancreatitis can result in both pancreatic exocrine insufficiency and diabetes. Diabetes associated with pancreatitis is observed in up to 90% of patients depending on duration of chronic pancreatitis, according to a cohort study of more than two thousand patients.[22] Furthermore, chronic pancreatitis is the strongest identified risk factor for pancreatic ductal adenocarcinoma (PDAC) according to case series and increases the risk at least 13.3-fold.[23] Importantly, the risk for PDAC in patients with both pancreatitis and diabetes is increased 33-fold.[24] A study from the Karolinska University Hospital (Stockholm) found that subpopulations of patients are at the greatest risk for PDAC by following 581 patients with chronic pancreatitis from 2003 to 2018 using available electronic medical records.[25] The results show that patients with diabetes and a high body mass index or with pancreatic exocrine insufficiency and a low body mass index at diagnosis of chronic pancreatitis are at the greatest risk for PDAC. Patients with chronic pancreatitis have a shortened lifespan, with death most often occurring from causes unrelated to the pancreas.[1 4 15 26 27]

Environmental, genetic, and anatomic factors

Chronic pancreatitis is more common in men than in women for all causes of the diseases.[28] Of note, gallstone acute pancreatitis usually does not progress to recurrent and chronic pancreatitis unless gallstones remain untreated resulting in recurrent attacks that lead to chronic disease.[1] Alcohol misuse is the most common cause of chronic pancreatitis (box 1).[1] A review indicated that that a threshold of five drinks or more per day is associated with the development of chronic pancreatitis.[29] However, less than 5% of heavy drinkers develop chronic pancreatitis, suggesting that additional factors are involved in disease development. One additional factor is smoking. That is, smoking and drinking are common coexisting behaviors that combined may contribute to the development of chronic pancreatitis.[30] The risk of pancreatitis associated with current smoking was highest among men who consumed more than four drinks a day (hazard ratio 2.06, 95% confidence interval 1.28 to 3.30) according to a multiethnic cohort study.[31] Recent studies suggest that alcohol misuse and smoking act synergistically for the risk of chronic pancreatitis.[32]

Box 1: Risk factors to consider in patients with chronic pancreatitis

- Alcohol misuse
- Smoking
- Genetic alterations
- Duct obstruction
- Pancreas divisum

Hereditary pancreatitis represents a genetic cause of chronic pancreatitis. This disorder was first described in six family members over three generations.[33] The underlying genetic defect was discovered in 1996 as a gain of function mutation in the PRSS1 gene that codes for the key pancreatic digestive enzyme, trypsin.[34] These patients have early onset pancreatitis with recurrent attacks of acute pancreatitis and a family history of pancreatitis. Inheritance occurs as an autosomal dominant trait with variable expression.[35] Chronic pancreatitis is also associated with loss of function gene mutations. Examples include serine protease inhibitor Kazal-type 1 (SPINK1) and chymotrypsin C (CTRC) genes encoding for two different proteins that both inhibit trypsin activity.[36 37] Thus, both gain of function and loss of function mutations lead to increased activation of trypsin, pointing out the importance of trypsin in the pathogenesis of pancreatitis.

Of note, the mutations of PRSS1, SPINK1, and CTRC involve digestive enzymes in the acinar cell of the exocrine pancreas.[38] Genetic variants involving pancreatic ductal cell functions are also associated with progression of pancreatitis. The commonly associated variants are in the cystic fibrosis transmembrane regulator (CFTR). The physiologic importance of CFTR is that it is necessary for ductal ion and water secretion to carry digestive enzymes secreted by the acinar cells to the duodenum.[39] Mutations in CFTR are associated with chronic pancreatitis.[40] Also, studies have shown that alcohol misuse inhibits CFTR function, supporting a crucial role for normal ductal function in preventing pancreatitis.[41 42]

Recently, a functional coding mutation inTRPV6 (which encodes the transient receptor potential cation channel subfamily V member 6) was identified as a risk factor for the disease.[43-46] Importantly,

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functional mutations in TRPV6 often present in combination with other known risk factors including SPINK1, CTRC, and CFTR mutations.[45] These findings emphasize that genetic variants often function in combination to set the stage for development of disease.

Genetic testing for patients is now available and should be considered in those without an otherwise known cause for their disease. Finding a genetic variant that underlies a patient's disease is important as it enables them to explain their disease to care providers not familiar with the potential for genetic causes. For example, the knowledge can help to dispel the impression that they have chronic pancreatitis because of alcohol misuse and that they are drug seekers when asking for pain relief in an emergency setting. The knowledge also provides information for families to learn about genetic transmission. Finally, the testing will identify patients eligible for therapeutics that will be developed for specific genetic causes or consideration for pancreatectomy when the identified genetic abnormality is associated with an elevated risk for pancreatic cancer.

Ductal obstruction can occur from inflammatory strictures or tumors, which can progress from recurrent acute pancreatitis to chronic pancreatitis. Pancreas divisum is a common normal variant of ductal anatomy defined as non-fusion of the dorsal and ventral pancreatic ducts occurring in up to 7% of the general population. This anatomic variant means that most of the pancreatic secretions enter the duodenum through the smaller duct of Santorini, emptying into the duodenum through an accessory papilla. This anatomy is believed to increase pressure in the pancreatic duct, predisposing to pancreatitis. However, this concept is controversial, including the fact that patients with pancreas divisum and chronic pancreatitis may also have underlying genetic mutations, which may be involved in chronic pancreatitis pathogenesis.[47 48] Most experts believe that if pancreas divisum is involved in the pathogenesis of chronic pancreatitis, it may be a co-factor and not the sole causative factor.[47]

Finally, chronic pancreatitis can be a presentation of the multi-organ IgG4 related disorder referred to as autoimmune pancreatitis when the disorder involves the pancreas. Autoimmune pancreatitis can present as acute or chronic pancreatitis, but the most common clinical presentation is painless jaundice. Autoimmune pancreatitis more commonly occurs in patients over age 60 with a three to one male predominance. An increased concentration of circulating IgG4 is a serologic marker for autoimmune pancreatitis. This entity is important to identify as it is most often responsive to steroid treatment or alternatively to other immune modulators in steroid resistant cases.[48]

Mechanism of the fibro-inflammatory response and pain of chronic pancreatitis

The key histologic features of chronic pancreatitis include fibrosis, inflammation, and ductal changes with loss of acinar tissue and islets. The mechanisms of the fibro-inflammatory response and pain are interconnected by intercellular communications. The pathways described here are ones that we hypothesize are involved in the promotion of chronic pancreatitis. Important disorders in parenchymal cells of the pancreas that represent the acute injury response are reviewed elsewhere.[49] Many of these acute injury pathways are identified in chronic pancreatitis, indicating the continuum from acute forms to chronic forms of pancreatitis.[50] Experiments in animal models show that the pathogenesis of chronic pancreatitis is due to interactions with pancreatic stellate cells (PSCs) or activated macrophages. Transforming growth factor β (TGF-β) and Smad3 signaling play key roles in the fibro-inflammatory response and the pain of this pancreatic disease.[51 52]

In normal pancreas, PSCs are in a quiescent state, characterized by lipid droplets containing vitamin A in their cytoplasm and minimal production of fibrosing extracellular matrix protein production.[53] However, in the environment of inflamed pancreatic tissue, PSCs become activated and produce abundant extracellular matrix proteins leading to fibrosis as well as inflammatory cytokines,[54 55] which promote influx of myeloid cells and convert them to alternatively activated macrophages.[52] These macrophages sustain the activated state of PSCs by secreting TGF-β, creating a feed-forward process by the fibro-inflammatory state of PSCs.[52] Two specific cytokines, interleukin 4 and interleukin 13, secreted by activated PSCs, stimulate the conversion of monocytes and macrophages to their alternatively active state, which secrete prodigious amounts of TGF-β.[52] Of note, the role of TGF-β in the fibro-inflammatory response of chronic pancreatitis is well established.[56-58] The TGF-β secreted by the macrophage maintains the PSC in its activated state, promoting more secretion of interleukins 4 and 13.[52] This interplay between activated PSCs and alternatively activated macrophages creates a feed-forward process promoting the fibro-inflammatory response of chronic pancreatitis,[52] and it provides for the production of TGF-β that mediates the pain of these pancreatic diseases by direct effects on sensory neurons in the pancreas mediated by SMAD3 signaling in the sensory neuron.[51] The role of TGF-β in the mechanism of pain may represent one of many pathways involved. For example, studies show that chronic pancreatitis causes reorganization of brain networks, with involvement of alterations in descending inhibitory pathways and metabolic disturbances.[59-62]

Figure 1 shows the pathways described here. Agents that interrupt one or more nodes in these pathways will have a benefit for treatment in chronic pancreatitis. Of note, because chronic pancreatitis results from recurrent episodes of acute pancreatitis, agents that can beneficially affect mechanisms of acute pancreatitis may have a role in chronic pancreatitis. An example is use of Orai-1 inhibitor therapy currently under investigation for acute

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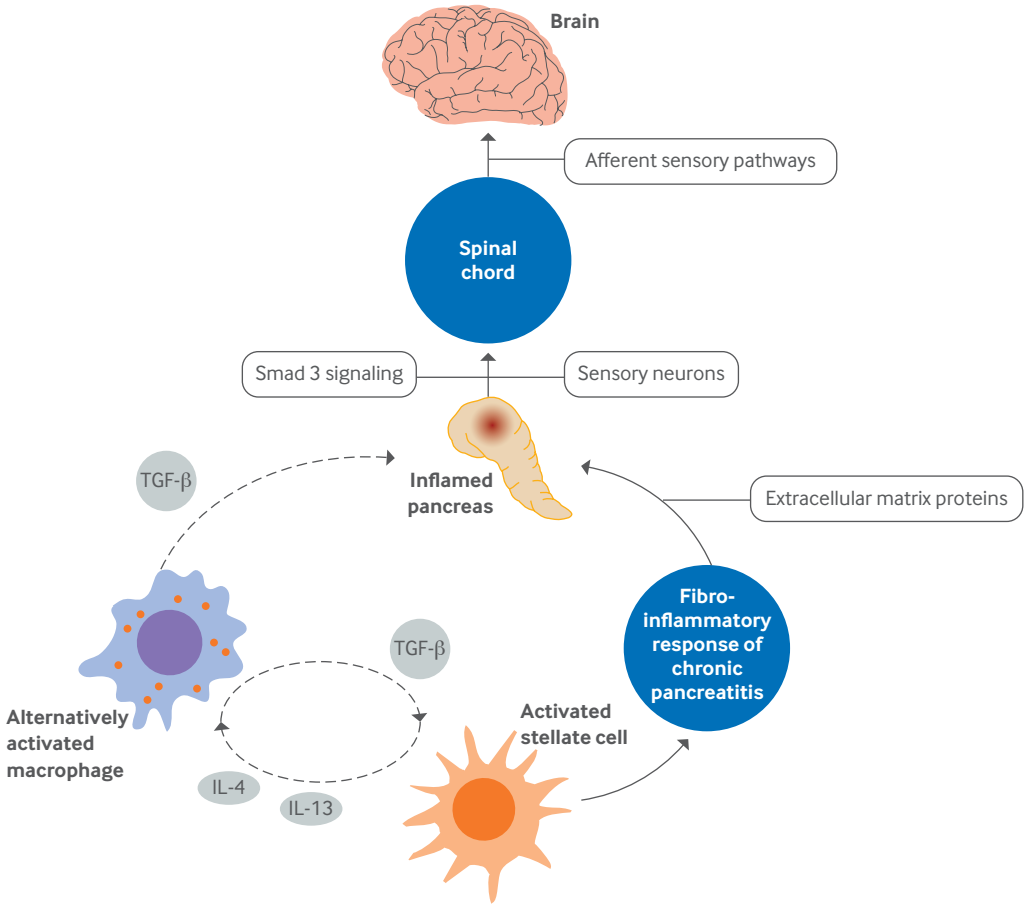

Fig 1 | Pathways of inflammatory, fibrosis, and pain response of chronic pancreatitis. In the environment of inflamed pancreatic tissue, pancreatic stellate cells (PSCs) become activated. Interleukin (IL)-4 and IL-13, secreted by activated PSCs, stimulate the conversion of macrophages to their alternatively active state. These macrophages sustain the activated state of PSCs by secreting transforming growth factor β-1 (TGF-β), advancing the fibro-inflammatory state of chronic pancreatitis. TGF-β mediates pain via intracellular Smad3 signaling in sensory neurons in the pancreas. We hypothesize that agents that interfere with one or more nodes in this scheme may provide treatment benefit for patients with chronic pancreatitis

pancreatitis.[63-65] A role also exists for lymphoid cells in addition to myeloid cells in chronic pancreatitis.[66] A recent study showed that molecules in cigarette smoke acting through the aryl hydrocarbon receptor on T cells cause stimulation of PSCs to promote fibrosis through the interleukin 22 pathway.[67] These findings again show an important interplay between inflammatory and immune cells and PSCs in the pathogenesis of chronic pancreatitis. The relative roles for myeloid and lymphoid cells in the pathogenesis of chronic pancreatitis may depend on the causative factors of the disease.

Diagnosis of chronic pancreatitis

The diagnosis of chronic pancreatitis is based largely on imaging; it is associated with calcification and pancreatic duct abnormalities in advanced cases but can be challenging in less advanced cases (box 2). In contrast to acute pancreatitis, which is defined by increases in serum amylase and lipase concentrations with abdominal pain typical of pancreatitis, these pancreatic enzymes are often not elevated in pancreatitis even with an exacerbation. The reason is a loss of functional pancreatic tissue containing these enzymes with chronic pancreatitis.[68] Circulating biomarkers for the diagnosis of chronic pancreatitis are not established. However, the Consortium on Chronic Pancreatitis, Diabetes and Pancreatic Cancer is making a significant effort to develop biomarkers to aid in diagnosis.[69-71]

Imaging plays a principal role in diagnosing chronic pancreatitis because of the absence of circulating biomarkers and reluctance to do risky pancreatic biopsies.[72] Among imaging modalities available for the diagnosis, computed tomography and magnetic resonance imaging (MRI) are the initial studies used for the evaluation of abdominal pain with chronic pancreatitis as a potential cause. Consistent with this practice, an expert panel of the American College of Gastroenterology published guidelines that recommend computed tomography or MRI for the first line diagnosis of chronic pancreatitis, suggesting that "either test should be the first choice for the diagnosis of chronic pancreatitis."[73] The panel further stated that "endoscopic ultrasonography (EUS), because of its invasiveness and lack of specificity, should be used only if the diagnosis is in question after cross-sectional imaging

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Box 2: Approaches to diagnosis and characterization of chronic pancreatitis

- Determine previous episodes of pancreatitis
- Obtain symptoms and environmental risk history
- Test for presence of exocrine insufficiency
- Obtain cross sectional imaging (computed tomography or magnetic resonance imaging)
- Monitor for diabetes
- In selected cases:
  - Endoscopic ultrasonography
  - Endoscopic retrograde cholangiopancreatography
  - Genetic testing
  - Pancreatic biopsy

is performed." The panel noted that other imaging modalities such transcutaneous ultrasonography, endoscopic retrograde cholangiopancreatography (ERCP), pancreatic elastography, and contrast enhanced endoscopic ultrasonography are potential imaging methods for diagnosis;[74-78] "high-quality randomized controlled trial evidence is not available to warrant their inclusion as first-line diagnostic tests for chronic pancreatitis in place of cross-sectional imaging or EUS."

Features of chronic pancreatitis on computed tomography include calcifications and atrophy and pancreatic duct dilations (fig 2). MRI and magnetic resonance cholangiopancreatography (MRCP) have an additional advantage of detecting ductal changes in addition to parenchymal changes.[79 80] Also, the administration of secretin to stimulate fluid secretion during an MRCP can further define pancreatic function and ductal pathology.[81-84] Of note, in addition to developing circulating biomarkers for the diagnosis of chronic pancreatitis, the Consortium on Chronic Pancreatitis, Diabetes and Pancreatic Cancer is greatly involved in advancing quantitative MRI for improved diagnostic ability in different stages of chronic pancreatitis, taking advantage of the unique T1 relaxation of the pancreas owing to its high protein content and the ability of MRI to measure extracellular volume (equivalent to fibrosis) and the presence of fat.[70 85 86] The envisioned goal is to approximate tissue histology with MRI measures.[87]

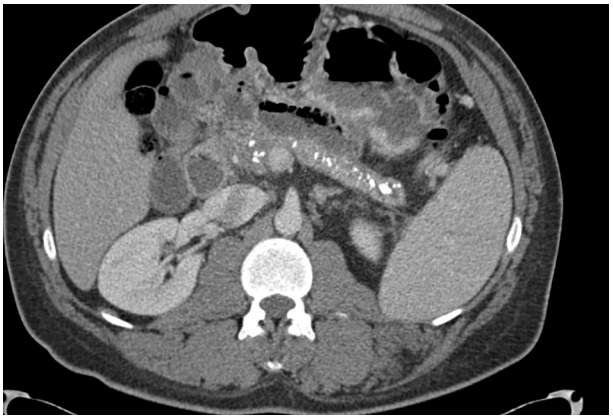

Fig 2 | Abdominal computed tomography scan of patient with chronic pancreatitis, showing calcifications and dilation of the pancreatic duct, especially in the tail

In cases in which morphologic evidence of pancreatitis is still needed despite the studies listed above, endoscopic ultrasonography of the pancreas can be used to identify disease at an early stage or with minimal change. Criteria for diagnosis by endoscopic ultrasonography include hyperechoic foci, hyperechoic strands, lobular contour, and cysts of the parenchyma, as well as ductal features of main duct dilatation, duct irregularity, hyperechoic duct margins visible side branches, and stones.[69] Finally, in patients whose diagnosis remains in question, histologic examination of a pancreatic biopsy is appropriate.

Of particular importance is the state of disease when no morphologic evidence is found using the imaging technology listed above. This state is often referred to as early chronic pancreatitis.[88] Further research is needed to develop molecular and/or imaging biomarkers associated with genetic and environmental risks to better identify patients with this state. Importantly for establishing the diagnosis, chronic pancreatitis is a clinical diagnosis that requires integration of clinical information including risk factors (genetics as appropriate) and exclusion of other disorders in the differential diagnosis together with the validation of imaging studies.

Relation between cause of chronic pancreatitis and potential complications

A cross sectional study of 1071 patients with chronic pancreatitis did a cluster analysis between the causes of pancreatitis and types of complications.[89] The analysis showed that complications potentially resulting from the continuing inflammatory process such as pseudocysts, ascites, pleural effusion, pancreatic fistula, and portal or splenic vein thrombosis are more likely with alcohol misuse related pancreatitis than with non-alcohol misuse related causes of pancreatitis (odds ratio 2.00, 95% confidence interval 1.38 to 2.90; P<0.001). On the other hand, fibrosing complications such as pancreatic duct lesions, common bile duct stenosis, and duodenal stenosis (odds ratio 2.23, 1.56 to 2.32; P<0.001) and complications such as exocrine pancreatic insufficiency (odds ratio 1.42, 1.00 to 2.01; P=0.046) were more likely associated with smoking.

Exocrine and endocrine insufficiency: identification and treatment

Failure of exocrine and endocrine function are common consequences of chronic pancreatitis. Pancreatic exocrine insufficiency (PEI) occurs when more than 90% of exocrine pancreatic function is lost, resulting in steatorrhea.[90] Patients with steatorrhea have oily or greasy stools and may describe bulky, pale, foul smelling, and/or floating stools. Additionally, the patient may have weight loss and fat soluble vitamin deficiency despite normal caloric intake. The classic measurement of fat in the stools collected for 72 hours in a person ingesting a diet adequate in fat (70-100 g/day) is considered an effective means of diagnosing

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steatorrhea. Normally, 7% or less of ingested fat appears in the stool. A simple qualitative microscopic examination of a single stool for oil is almost as sensitive as quantitative measurements for fat, making the measurement of steatorrhea more accessible.[91 92] Additional practical tests for PEI include measurements of fecal chymotrypsin and elastase-1. Both enzymes are produced by the pancreas and remain constant throughout the gastrointestinal tract. Elastase-1 has been shown to be more specific than chymotrypsin, with sensitivity approaching 100% for significant insufficiency.[93 94] Measurement of serum trypsin has also been shown to associate with severe PEI.[95]

In contrast to the widely available methods listed above for diagnosis of PEI, specialized centers may provide direct testing of pancreatic function, which can be useful in diagnosing chronic pancreatitis. In these tests, the exocrine pancreas is stimulated with a secretagogue such as secretin for testing ductal function or cholecystokinin for testing acinar function, followed by measurement of the volume and concentration of analytes into the duodenum collected by aspiration with a duodenal tube designed to prevent interference with gastric secretions or an endoscope aspirating at site of the pancreatic outflow into the duodenum.[96-98] Currently, testing the ductal function with secretin stimulation and measurement of peak bicarbonate concentration prevails over testing acinar function with cholecystokinin stimulation.

Treatment of PEI is essential to reverse and prevent its consequences, which include weight loss, fat soluble vitamin deficiency, metabolic bone disease, and sarcopenia.[99] Osteoporosis and osteopenia are highly prevalent in this population and are associated with an increased risk of fractures.[100-102] A recommended starting dose 40 000–50 000 USP units of lipase taken with each meal is recommended.[99] Treatment monitoring includes improvements in steatorrhea, weight, fat soluble vitamins, and measures of bone density and muscle mass. Dose adjustments may be necessary.

Endocrine insufficiency manifested as diabetes mellitus can occur in chronic pancreatitis.[103-106] This form of diabetes mellitus is referred to as diabetes of the exocrine pancreas, pancreatogenic diabetes, post-pancreatitis diabetes (PPDM) or type 3c diabetes. The mechanism of this form of diabetes mellitus, differences from type 1 and type 2 diabetes mellitus, and the most appropriate approach to treatment are under intensive investigation.[103 104 107-111] PPDM is generally managed by starting with metformin, but insulin may eventually be needed. Incretin therapy is avoided considering the risk of pancreatitis. Patients with PPDM have an added complexity for management. That is, these patients need consistent treatment of PEI to ensure nutrient absorption for prevention of hypoglycemia and additional vigilance to prevent hypoglycemia because of potential loss of counter-regulatory glucagon secretion.

Interventions for pain

Pain is the most common manifestation of chronic pancreatitis and can be debilitating and unrelenting.[112-114] Moreover, the pain of chronic pancreatitis is associated with debilitation in several physical, mental, and social health outcomes.[64 67 115 116] Patients experience epigastric or mid-abdominal pain, which can be accompanied by back pain. The cause is the presence of inflammatory mediators, which increase interstitial pressure leading to diminished blood perfusion, low oxygen tension, and consistent gland inflammation.[37] These symptoms may be constant or intermittent and exacerbated by a meal, and it is important to consider alternate diagnoses including peptic ulcer disease, complications of pancreatitis, and cancer, which these patients develop at higher rates than those without chronic pancreatitis.

Medical management of pain

Abstinence from alcohol and smoking should be recommended, and support programs to facilitate this should be offered. Abstinence will extend life and slow the evolution of chronic pancreatitis but not stop it. Smoking increases the risk of developing pancreatic cancer and accelerates chronic pancreatitis. A meta-analysis of 10 case-control studies and two cohort studies including 1705 patients identified a dose-response effect of tobacco on risk of chronic pancreatitis (odds ratio one pack 2.4 (95% confidence interval 0.9 to 6.6); more than one pack 3.3 (1.4 to 7.9). This risk was diminished with smoking cessation.[115]

Analgesics provide treatment for pain from chronic pancreatitis and include non-opioid and opioid medications. Non-opioids are recommended as first line therapy and opioids for worsening and persistent pain. When the patient transitions to consistent opioid use, management by a chronic pain specialist should be started.

Adjunctive medications including tricyclic gabapentinoids, antidepressants, and selective serotonin reuptake inhibitors can decrease opioid requirements and treat neuropathic pain. An RCT that randomized 64 patients to pregabalin or placebo for three weeks found that pregabalin significantly improved pain relief (36% *v* 24%; P=0.02).[117] Antioxidant therapy has been used in chronic pancreatitis with varying results. A Cochrane review including 12 RCTs and involving 585 patients concluded that pain was less in the antioxidant group (mean difference −0.33, 95% confidence interval −0.64 to −0.02).[118]

Pancreatic enzyme replacement therapy has long been used to decrease pain from chronic pancreatitis despite little evidence to support this. To date, nine clinical trials, seven of them randomized, have shown inconsistent data on pain; because of this, enzyme replacement is not recommended to treat this symptom.[116 119-125]

Celiac plexus blockade has varying efficacy as reported in the literature. The procedure involves the

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injection of local anesthetic and a steroid into the celiac ganglia and can be done under endoscopic ultrasound guidance, percutaneously, or directly during surgery. A meta-analysis of six studies including randomized studies, prospective studies, and case series evaluating endoscopic guided block estimated that pain relief based on validated pain score assessment or decrease in opioid use was 51.46%.[126] For patients who have exhausted medical management of pain, a celiac plexus blockade should be considered. However, the pain relief is usually transient.

Endoscopic treatment

Chronic pancreatitis can cause strictures of the main pancreatic duct and stone formation contributing to diminished flow, inflammation, and pain. For patients with a dilated duct, endoscopic or surgical techniques to decompress the duct can relieve pain and may preserve pancreatic exocrine and endocrine function.

Endoscopic treatment of pain in patients with pancreatic duct strictures and stones is feasible, and some patients may benefit from long term pancreatic duct stenting to manage pancreatic duct strictures. A meta-analysis of 13 studies involving 298 patients found that pain improved by 89% after pancreatic stent compared with before stenting.[127] A randomized trial comparing endoscopy and lithotripsy with lithotripsy alone found a similar decrease in the number of pain episodes per year (mean decrease 3.7, 95% confidence interval 2.6 to 4.9; P<0.001) over a four year period, suggesting that lithotripsy alone is sufficient.[128]

Surgical approaches to chronic pancreatitis

Surgery for pain from chronic pancreatitis is generally reserved for patients with severe disease manifested by substantial and longstanding symptoms in the presence of pancreatic duct dilation or stones. Surgery for chronic pancreatitis may be performed safely and with minimal perioperative morbidity or mortality. Several operations have been developed whereby varying amounts of the pancreas are removed to ensure improved drainage of pancreatic fluid from the duct to the gastrointestinal tract. To maintain exocrine and endocrine pancreatic function, most modern procedures are parenchyma sparing approaches rather than a pancreatectomy, unless this is done concomitantly with an islet cell transplant. These surgeries include a pancreatoduodenectomy (Whipple), duodenum preserving pancreatic head resection (Frey and Beger/Berne), distal pancreatectomy, and drainage procedures such as longitudinal pancreatojejunostomy (Puestow) (fig 3). The operation recommended is based on the pancreatic duct anatomy and distribution of the disease in the gland.

Eleven RCTs have compared different dyads of operations for chronic pancreatitis pain. When the pancreatic head is removed patients have the best outcomes related to pain, and if the duodenum can be preserved pancreatic function and quality of life seem to be improved. This is especially true when most of the disease is limited to the head. A meta-analysis of four trials included 173 patients who had a duodenum preserving pancreatic head resection or pancreatoduodenctomy for pain relief in chronic pancreatitis. In this analysis, the duodenum preserving approach showed no difference in pain relief (odds ratio 1.08, 95% confidence interval 0.88 to 1.33) or endocrine insufficiency (odds ratio 0.49, 0.22 to 1.09), but the duodenal preserving procedure had less exocrine insufficiency (odds ratio 0.20, 0.06 to 0.66) and improved quality of life (weighted mean difference 25.07, 18.83 to 31.21).[129] The follow-up ChroPac trial randomized 250 patients to pancreatoduodenectomy or duodenum preserving pancreatic head resection and found no difference in quality of life at 24 months, which included an assessment of pain.[130]

Most long term studies report that 60-80% of patients have improvement in pain following surgery. Although duodenum preserving pancreatic head resection is a more complicated procedure than a longitudinal pancreatojejunostomy, some types of parenchymal resection such as a Frey procedure that completely exposes the duct and allows for all stones to be removed is essential to secure the best pain relief. A tailored approach accounting for the distribution of the pancreatic inflammation, ductal anatomy, and patient's condition should be used to determine the optimal operation for each patient.

Total pancreatectomy with islet autotransplantation

In patients with painful chronic pancreatitis who have exhausted medical management and completed endoscopic or surgical intervention, total pancreatectomy offers an option to tackle pain by removing the entire gland, the source of the inflammatory pain cascade. This is also an option for patients with hereditary pancreatitis who have a substantial increase in risk for pancreatic cancer. A pancreatectomy accompanied by an islet autotransplantation of islet isolated from the resected gland and infused into the liver via the portal vein promises improved glucose homeostasis after the procedure. This procedure is appropriate for patients with normally functioning islets before the surgery. The available data to support this approach come from observational series. The Dutch Pancreatitis Study Group published a meta-analysis of 15 observational studies including 1255 patients, and at one year after surgery the opioid-free rate had improved from between 0% and 15% to 63% (95% confidence interval 46% to 77%) and the insulin-free rate had decreased from between 89.5% and 100% to 30% (20% to 43%).[131] In patients who have no other options and have access to a skilled center providing this service, total pancreatectomy with islet autotransplantation is a reasonable approach to manage pain from chronic pancreatitis.

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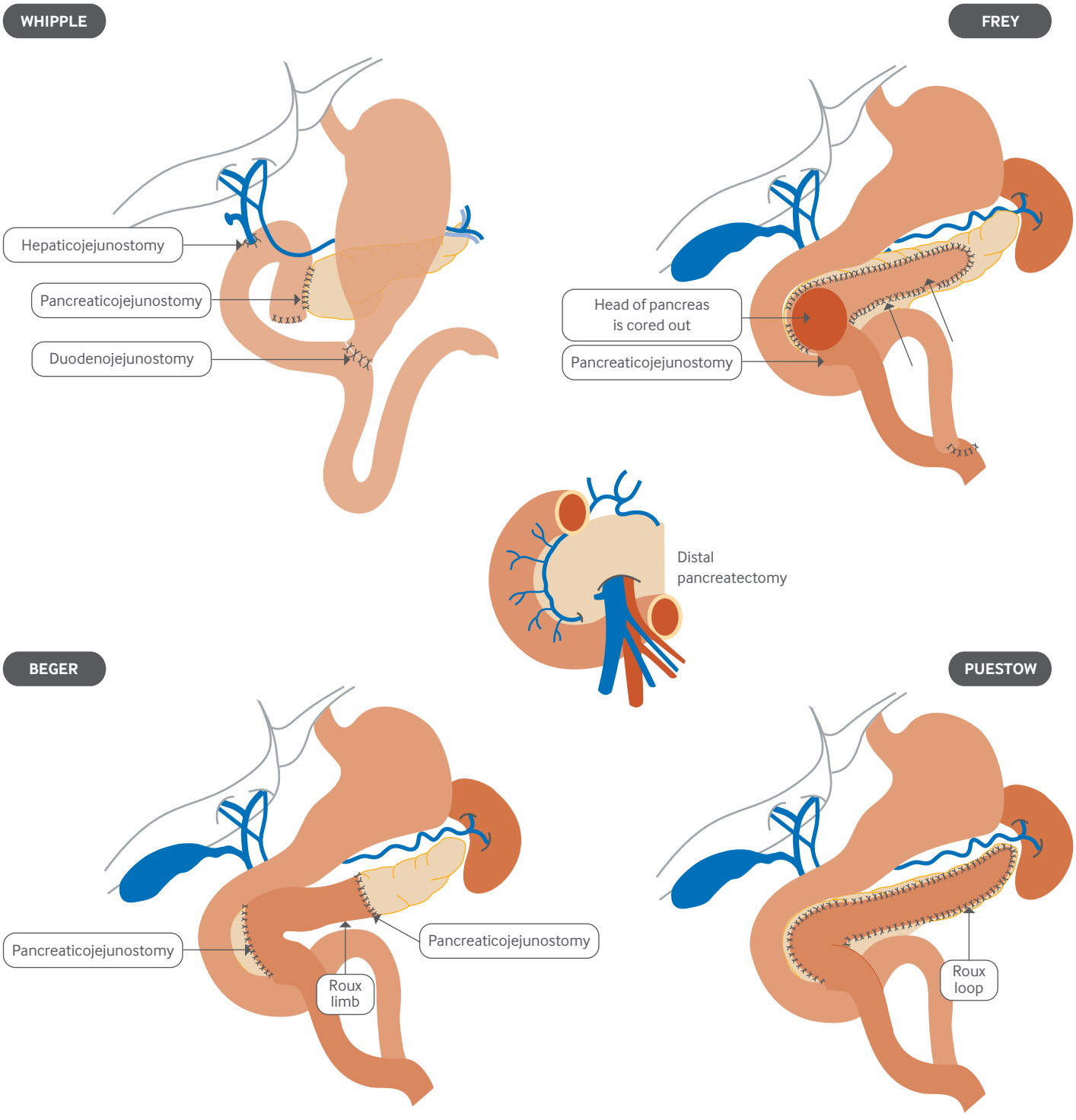

Fig 3 | Pancreatoduodenectomy (Whipple), duodenum preserving pancreatic head resection (Frey and Beger/Berne), distal pancreatectomy, and longitudinal pancreatojejunostomy (Peustow)

Endoscopic versus operative approaches

Evidence from randomized trials suggests that surgery should be considered over endoscopic therapy for the long term treatment of painful chronic pancreatitis with ductal obstruction. Three RCTs investigating endoscopic and surgical treatment of pain have been completed and concluded that surgery was superior to endoscopic techniques. Recent practice guidelines from both the American College of Gastroenterology and the American Gastroenterological Association include this recommendation based on what each judged to be moderate to strong evidence.[53 114]

The first RCT randomized 140 patients to endoscopic treatment including sphincterotomy, stenting, and stone removal or surgery.[132] The initial outcomes related to pain were similar, but

doi: 10.1136/bmj-2023-070920 | *BMJ* 2024;384:e070920 | the bmj

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at five years complete absence of pain was twice as high in the surgery group (37% *v* 14%) and partial relief was similar (49% *v* 51%). In addition, patients who underwent surgery had improved increased body weight measurements, and the incidence of new onset diabetes was no different (34-43%). The authors concluded that surgery was superior to endotherapy and that endotherapy could be offered as initial treatment followed by surgery in cases in which pain persisted.

Two years later, an RCT from the Netherlands was published, which randomized 39 patients between endoscopic treatment and lithotripsy or pancreatojejunostomy that included removal of some pancreatic parenchyma. Patients who had surgery reported lower pain scores (P<0.001) and better physical health (P=0.003). Striking pain relief was seen in 75% of surgery patients and only 32% of the endoscopic group (P=0.007), and the endoscopic group received eight interventions whereas the surgery patients had three.[133]

The third RCT, the ESCAPE trial from the Dutch Pancreatitis Study Group published in 2020, led to the current guideline recommendations.[134] This multicenter RCT included 88 patients and compared best medical management with endoscopic treatment versus upfront surgery for painful chronic pancreatitis. Pain scores were significantly better in the surgery group (Izbicki pain score 37 *v* 49; −12 points, 95% confidence interval −22 to −2; P=0.02), and pain relief was achieved in 58% of surgery patients versus 39% of the endoscopy group (P=0.10). Pancreatic function, complication rates, and quality of life were similar between groups. An important consideration of this study is that when the duct was cleared endoscopically, pain was improved at a similar rate between treatment arms. It was notable that pain was not better in 62% of the patients in the endoscopy group, and half of this group ultimately had surgery to manage this. This trial provides the strongest evidence to date informing treatment of chronic pancreatitis in patients with a dilated pancreatic duct and stones and pain. A Cochrane review found that surgery offers a higher likelihood of pain relief than endoscopic treatment in the medium term (2-5 years: risk ratio 1.62, 1.22 to 2.15) and at long-term follow-up (≥5 years: 1.56, 1.18 to 2.05).[135] With this evidence, surgery should be considered early in the management of these patients.

Fig 4 | Abdominal computed tomography scan showing a pancreatic pseudocyst expanded anteriorly against the stomach

Complications of chronic pancreatitis

Pancreatic pseudocysts and acute fluid collection occur in patients with chronic pancreatitis owing to exacerbations of inflammation and ductal disruption. Pseudocysts are less likely to resolve in chronic pancreatitis because this condition does not spontaneously resolve as it does in acute pancreatitis, so invention is more commonly needed (fig 4). Patients with symptomatic collections resulting in pain, gastric or duodenal obstruction with weight loss, or biliary obstruction should undergo endoscopic ultrasound guided transgastric or transduodenal drainage with plastic stents or lumen apposing metal stents. Alternatively, transpapillary drainage can be attempted. However, a meta-analysis including 1355 patients found that success using transmural drainage and resolution of the pseudocyst was substantially higher than that using a transpapillary approach (90.6% (95% confidence interval 81.0% to 95.6%) versus 58.5% (36.7% to 77.4%)).[136] Transpapillary drainage has been successfully deployed for a disconnected pancreatic duct. The same study showed that surgical drainage results in success rates comparable to those of endoscopic treatment (82% (68.6% to 90.5%) versus 87.4% (81.2% to 91.8%); P=0.389). Percutaneous drainage is largely ineffective with very high recurrence rates, particularly in chronic pancreatitis. As the morbidity of endoscopic drainage is substantially less than with surgery, this method is the recommended treatment for pseudocysts in chronic pancreatitis.

Biliary stricture occurs in 10-15% of patients with chronic pancreatitis, and the first concern should be to rule out the possibility of malignancy with imaging and endoscopic ultrasound guided biopsy. Benign biliary strictures typically have a tapered appearance on cholangiography. Once malignancy has been excluded, endoscopic, surgical, and interventional radiologic techniques are available to treat the stricture. RCT data suggest that endoscopic treatment is reliable. One study enrolled 60 patients to self-expandable metallic stent versus plastic stent and showed a two year, stricture-free success rate of 90% (72% to 97%) in the plastic stent group and 92% (70% to 98%) in the metal stent group.[137] Similar success rates were seen in an RCT using stents for benign biliary stricture (92.6%).[138] Additionally, if the patient is having surgery for chronic pancreatitis, a biliary bypass or decompression of the bile duct with the pancreatic operation can be safely performed with outstanding long term resolution of the stricture.

Vascular complications of chronic pancreatitis include pseudoaneurysms of the surrounding arterial vessels, particularly the splenic artery, or

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venous thrombosis. A meta-analysis of endovascular embolization for pseudoaneurysms in pancreatitis including 29 studies and 849 patients found a clinical success rate of 88% (83% to 91%; I^2=0%) at 12 months.[139] Splenic infarction was the most common complication, seen in 5.5% of patients, which nearly always resolves. Patients with thrombosis of the splenic vein can usually be managed expectantly, but left sided portal hypertension manifested by gastric bleeding may occur in up to 12.3% according to a meta-analysis of 99 reports including 805 patients.[140] For these patients, splenic artery embolization may be therapeutic and splenectomy definitive.

Differentiating chronic pancreatitis from cancer

Determining whether a patient has pancreatic cancer in the setting of chronic pancreatitis is challenging. Maintaining vigilance for the possibility of pancreatic cancer with frequent assessment and ultimately no diagnosis of cancer is a common approach. One pooled analysis of 13 studies found that a nearly eightfold risk for cancer at five years from diagnosis of chronic pancreatitis diminished to 3.5-fold after nine years (7.90 (95% confidence interval 4.26 to 14.66) and 3.53 (1.69 to 7.38)).[141] In other words, if the patient has not developed cancer over time while under medical supervision the risk of doing so decreases. However, the establishment of true risk is difficult because some patients may have been misclassified as having chronic pancreatitis when in fact cancer is present. Chronic inflammation is known to contribute to carcinogenesis. Imaging with computed tomography, MRI, and endoscopic ultrasonography assists in identifying a suspicious lesion that should be biopsied at the time of endoscopic ultrasonography to determine the diagnosis. CA 19-9 can be elevated in chronic pancreatitis, especially with biliary obstruction, but elevation increases the suspicion of pancreatic cancer. A pooled analysis of the ability of CA 19-9 concentration to differentiate pancreatic cancer from chronic pancreatitis that included 3125 patients showed a sensitivity of 0.81 (95% confidence interval 0.80 to 0.83), a specificity of 0.81 (0.79 to 0.82), a positive likelihood ratio of 4.08 (3.39 to 4.91), a negative likelihood ratio of 0.24 (0.21 to 0.28), and a diagnostic odds ratio of 19.31 (14.40 to 25.90).[142] Patients with hereditary pancreatitis should be entered into a screening program with yearly imaging and consideration for pancreatectomy.

Emerging treatments

Understanding of the mechanisms of chronic pancreatitis is revealing potential therapeutic approaches in animal models of chronic pancreatitis, which are being applied in human clinical trials. For example, inhibition of the effects of interleukins 4 and 13 has been shown to decrease chronic pancreatitis.[52] Pirfenidone, an agent that inhibits TGF-β actions to promote fibrosis and is approved by the US Food and Drug Administration for treatment of idiopathic pulmonary fibrosis, has shown benefit in models of chronic pancreatitis.[143] Simvastatin, by inhibiting the inflammatory response of pancreatitis through correcting autophagic mechanisms of the acinar disordered in pancreatitis, has the potential for therapeutic benefit in chronic pancreatitis and is in clinical trials (ClinicalTrials.gov NCT04021498 and NCT02743364).[144-148] Another potential mechanism based therapeutic agent is a highly potent vitamin D analog, paricalcitol, which returns activated PSCs to their quiescent state and which is in an early clinical trial (NCT05664880).[149 150]

Management summary and guidelines

Box 3 provides a summary list of key management actions for patients with chronic pancreatitis based on this review). Box 4 provides a list of guidelines and consensus statements that provide further details for the diagnosis and management of chronic pancreatitis.

Box 3: Management of patients with chronic pancreatitis

- Stop alcohol use and smoking
- Monitor and treat exocrine insufficiency and diabetes
- Maintain nutritional intake
- Monitor for macro-nutritional and micro-nutritional deficiencies
- Monitor bone health
- Consider dietary alterations
- Use analgesics safely
- In selected cases:
  - Endoscopic treatments
  - Surgical treatments
  - Total pancreatectomy with islet autotransplantation

Box 4: Published guidelines and consensus statements for chronic pancreatitis

- Guidelines for Risk Factors in Chronic Pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[151]
- Clinical Guideline for Chronic Pancreatitis
  - American College of Gastroenterology[73]
- Clinical Practice Guidelines for Chronic Pancreatitis
  - Japanese Society of Gastroenterology[152]

doi: 10.1136/bmj-2023-070920 | *BMJ* 2024;384:e070920 | the bmj

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- Harmonizing diagnosis and treatment of Chronic Pancreatitis across Europe.
  - Working Group on Harmonizing the diagnosis and treatment of chronic pancreatitis across Europe of the United European Gastroenterology[153]
- Evidence-based Guidelines for the diagnosis and therapy of Chronic Pancreatitis
  - United European Gastroenterology[154]
- International consensus statements on early Chronic Pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[88]
- Guidelines for the Diagnostic Cross-Sectional Imaging and Severity Scoring of Chronic Pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[155]
- Guidelines on the role of diagnostic endoscopic ultrasound in the management of Chronic Pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[156]
- Guidelines on the histopathology of Chronic Pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[157]
- Diagnosis and treatment of exocrine pancreatic insufficiency in Chronic Pancreatitis
  - An international expert survey for the Dutch Pancreatitis Study Group[158]
- Consensus Guidelines for the management of pain of Chronic Pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[60]
- Guidelines on interventional endoscopy in chronic pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[159]
- Guideline on clinical nutrition in acute and chronic pancreatitis
  - European Society for Clinical Nutrition and Metabolism[160]
- Consensus guidelines for surgery and the timing of intervention in chronic pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[161]
- The role of total pancreatectomy with islet autotransplantation in the treatment of chronic pancreatitis
  - A report from the International Consensus Guidelines in chronic pancreatitis[162]
- Guidelines on surveillance for pancreatic cancer in chronic pancreatitis
  - International Consensus Guidelines Working Group for Chronic Pancreatitis in collaboration with the International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society and European Pancreatic Club[163]

Conclusion

Chronic pancreatitis remains a vexing condition with some partially effective treatments to reduce symptoms and complications but no cure. Multiple approaches to improve outcome are underway. ClinicalTrials.gov lists 210 studies for chronic pancreatitis. As the pathobiology of this disease continues to be defined, we hope that future research may find a cure.

GLOSSARY OF ABBREVIATIONS

- CFTR—cystic fibrosis transmembrane regulator
- CTRC—chymotrypsin C
- ERCP—endoscopic retrograde cholangiopancreatography
- MRCP—magnetic resonance cholangiopancreatography
- MRI—magnetic resonance imaging
- PDAC—pancreatic ductal adenocarcinoma
- PEI—pancreatic exocrine insufficiency
- PPDM—post-pancreatitis diabetes
- PSC—pancreatic stellate cell
- RCT—randomized controlled trial
- SPINK1—serine protease inhibitor Kazal-type 1
- TGF-β—transforming growth factor β

QUESTIONS FOR FUTURE RESEARCH

- What are the mechanisms to inhibit and reverse the fibro-inflammatory process underlying chronic pancreatitis?
- How do we develop and evaluate additional agents for preventing the progression and treating chronic pancreatitis?
- Can we establish reliable and simple tests to establish the diagnosis of both chronic pancreatitis and exocrine pancreatic insufficiency?
- How can we determine the long term nutritional and metabolic consequences of chronic pancreatitis, and how should these be managed and prevented?
- What new medications and interventions will be most effective in treating pain from chronic pancreatitis considering subpopulations of patients with chronic pancreatitis with potentially different pain mechanisms?

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HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS MANUSCRIPT

This work was reviewed by Mission:Cure (https://mission-cure.org), which is a community of patients, families, scientists, clinicians, and generous supporters, driving new research, accelerating drug discovery and development and creating hope for improved quality of life for patients with chronic pancreatitis. The reviewing organization agreed with the article and made minimal edits.

Contributors: OJH and SP contributed to the planning, conduct, writing, editing, and reporting of this article and are equally responsible for the overall content as guarantors.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned; externally peer reviewed.

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